REMARKS

Applicant respectfully requests reconsideration. Claims 25-27, 29-35, and 37 were previously pending in this application. Claim 25 has been amended to recite that the individual is not fully responsive to conventional therapy. Support for this amendment can be found, for example, on page 1, lines 26 – 28; page 2, lines 19 - 23 and Example 1. Claim 27 has been cancelled. New claim 38 has been added. As a result, claims 25-26, 29-35, 37 and 38 are now pending for examination; claim 25 is an independent claim. No new matter has been added.

Claim Rejections Under 35 U.S.C. §112

Claims 25-27, 29-35, and 37 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The Examiner alleges that "applicant did not specifically describe adjunctively treating major depressive disorder comprising exo-S-mecamylamine and additional agents."

Applicant disagrees with the Examiner's assessment and does not acquiesce in the rejection. Nevertheless, Applicant has amended claim 25 to delete the term "adjunctively" The rejection is, thus, moot. The function of the written description requirement is to ensure that the inventor had possession, as of the filing date of a patent application, of the specific subject matter claimed. The manner in which this is accomplished is not material and it is not necessary that there be word for word support for the claimed invention. The claimed subject matter need not be described literally in order for the disclosure to satisfy the written description requirement, so long as all claim limitations are supported in the specification through express, implicit or inherent disclosure (MPEP § 2163). A specification provides adequate written description if it allows those of ordinary skill in the art to recognize that the inventor was in possession of the claimed invention when the application was filed. Applicant has clearly described administration of exo-S-mecamylamine and at least one additional agent that is an agent for treating a mood disorder to an individual who is not fully responsive to conventional therapy. The specification as filed clearly shows that Applicant was in possession of the invention at the time the application was filed.

Rejections Under 35 U.S.C. §103

Claims 35, 27, 29-35, and 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Popik et al. (British Journal of Pharmacology, 2003, Vol. 139, pgs. 1196-1202, previously cited) in view of Fava (Biological Psychiatry, 2003, Vol. 52, pgs. 649-659) in view of Shytle et al. (U.S. 6,734,215 B2, previously cited).

The claimed invention is not taught or suggested by any of the cited references. The Examiner alleges that it would have been obvious for one of ordinary skill in the art to combine the teachings of Popik et al., Fava and Shytle et al. to arrive at the instant claims. Applicant respectfully disagrees and requests reconsideration of this rejection.

As the Examiner acknowledges, Popik et al. does "not specifically teach a method of adjunctively treating refractory major depression or refractory major depressive disorder" (page 6 of the Office Action). Importantly, the Examiner has not understood that the animal model on which Popik et al. relied clearly showed a dose-dependent response to the drug administered; animals exhibited a dose-dependent response to citalopram. That response to citalopram could be enhanced by sequential administration of mecamylamine. The Popik et al. model is not a model in which the animal is not fully responsive to the drug administered. The model used by Popik et al. is not a model of refractory major depressive disorder. This is made clear by Popik et al.: the mice responded to citalopram in a dose-dependent manner. The Examiner's attention is directed to pages 1198 – 1200. See, for example, page 1198, column 2: "In this experiment, citalopram (2 mg kg^{-1}) produced a significant effect on immobility, but coadministration of 0.8 mg kg^{-1} of nicotine did not significantly affect CIT effect." Also see page 1199, column 1: "In this set of experiments, CIT (2 mg kg^{-1}) significantly inhibited the immobility and this effect was further increased by MEC….." See further discussion of this response at page 1199 and also at page 1200. Further, there is no mention of or reference to refractory major depression by Popik et al. The results of the work simply show that in the tail-suspension test, citalopram responsive mice became more active when mecamylamine was administered than citalopram responsive mice who did not also receive mecamylamine.

The model used by Popik et al. exhibits a dose dependent response to citalopram and does not model a condition in which an individual is not fully responsive to conventional therapy. In contrast, it should be seen as a model of a condition in which a mouse responds in a dose-dependent manner.

The Examiner has combined Popik et al. with Fava and Shytle et al. In doing so, the Examiner states that Fava teaches that unipolar depression entails treatment resistant depression and "contends that to one of ordinary skill in the art at the time of the invention would have found it obvious to utilize the method of Popik et al. to treat refractory patients of major depression since Fava teaches that major depression entails resistant major depression patients who are non-responsive to adequate antidepressant therapy and Popik demonstrated effective treatment of major depression." (page 7 of the Office Action).

Applicant respectfully disagrees. As is readily apparent from the above discussion, the Popik et al. model is one in which the mice are responsive to SSRI therapy. It is not a model in which the animal is not fully responsive to the drug administered. Further, Popik et al. makes no reference to refractory depression, partial response or no response to conventional therapy.

Fava recognizes that treatment resistant depression (TRD) is a relatively common occurrence in clinical practice and needs to be addressed; explains that even obtaining an accurate and systematic assessment of TRD is a challenge to both clinicians and researchers; and points out that it is not possible to "be sure that the degree of response to antidepressant treatment is inadequate unless we have a careful and systematic assessment of depressive symptoms with validated instruments." (Page 653, column 2, bottom) Fava goes no further; it does not teach or propose use of a combination of therapies. There is no motivation to combine Popik et al. with Fava. If, despite the lack of motivation, the two references were combined, the result would not have been the claimed method. The Examiner's assessment is based upon impermissible hindsight and relies upon the referenced specification. Applicants have clearly demonstrated in humans that administration of mecamylamine in combination with SSRI to individuals who are partial responders to a conventional therapy (SSRI treatment) is effective in the treatment of refractory major depressive disorder. As discussed in Example 1, partial responders, based on Hamilton

Depression (HAM-D) scores, treated with mecamylamine and antidepressant were classified as responders at the end of an 8-week trial, as assessed by a 50% reduction in HAM-D scores. No members of the group of partial responders treated with placebo and antidepressant became responders, based on the same assessment. Fava is a broad discussion of diagnosis and definition of TRD. It provides no teaching of a predictable treatment of TRD. Fava discusses the need to consider contributing factors, such as medical and psychiatric comorbidity, as part of "[a] diagnostic re-evaluation [that] is essential to the proper management of these patients" and concludes that "very few criteria for TRD have been empirically tested." (Page 655, right column, bottom)

Shytle et al. describes use of exo-S-mecamylamine substantially free of exo-R-mecamylamine as an improved therapy for patients with nicotine-responsive neuropsychiatric disorders. It provides no teaching or motivation to combine exo-S-mecamylamine with an additional therapy for any purpose and provides no guidance or direction that would result in the use of a combination of exo-S-mecamylamine and antidepressant (adjunctive therapy with mecamylamine) for treatment of a depressive disorder of any type.

As discussed previously, the animal model used by Popik et al. exhibits a dose-dependent response to citalopram and does not model a condition in which an individual is not fully responsive to conventional therapy. The Popik et al. model is not a model of refractory depression. Fava addresses the need for better assessment and diagnosis of treatment-resistant depression and Shytle et al. describes an approach to treating nicotine-responsive neuropsychiatric disorders. The combination of mecamylamine with antidepressant to treat major depressive disorder in an individual not fully responsive to conventional therapy is described for the first time in Applicant's specification.

In order to reject a claim based on the rationale that combining prior art elements according to known methods yields predictable results, the Examiner must articulate a finding that one of ordinary skill in the art would have recognized that the results of the combination were predictable. MPEP 2143 (A). First, the cited references should not be combined. Further, the Examiner has not articulated why, if the references were combined, one of skill in the art would have recognized that the results of the combination of the teachings of Popik et al., Fava and Shytle et al. were

predictable. In the absence of Applicant's work, as described in the referenced application, it would not have been reasonable to predict, at the time of the invention, whether central nAChR antagonism has an effect on SSRI-treated refractory major depression or what that effect might be. Applicant has demonstrated that administration of mecamylamine in combination with SSRI to individuals who are partial responders to SSRI treatment was effective in the treatment of refractory major depressive disorder.

Accordingly, withdrawal of the rejection is respectfully requested.

Claim 26 is rejected under 35 U.S.C. 103(a) as being unpatentable over Popik et al. (British Journal of Pharmacology, 2003, Vol. 139, pgs. 1196-1202, previously cited) in view of Fava (Biological Psychiatry, 2003, Vol. 52, pgs. 649-659) in view of Shytle et al. (U.S. 6,734,215 B2, previously cited) as applied to claims 25, 27, 29-35 and 37 and in further view of Cassano et al. (Eur. Arch. Psychiatry Clin. Neurosci. 1993, Vol. 242, pgs. 373-380).

The Examiner alleges that it would have been obvious for one of ordinary skill in the art to have tried a modified method of Popik et al. in patients of single episode major depressive disorder, since Cassano et al. teach that such disorder does not last long and is less severe as compared to other major depressive disorders (page 11 of the Office Action). Applicant respectfully disagrees and traverses the rejection.

The teachings and deficiencies of Popik et al., Fava and Shytle have been discussed in response to the previous § 103 rejection. Even if the cited references are combined, they fail to provide the basis for a case of prima facie obviousness. Even if Cassano et al. is read as proposed by the Examiner, which Applicant disputes, Cassano et al. does not cure the deficiencies of Popik et al., Fava and Shytle et al., either alone or in combination. Cassano et al. investigated the characteristics of single episode major depression among a population of 687 depressive patients. In contrast, claim 26 relates to methods of treating refractory major depression by administering exo-S-mecamylamine in combination with at least one additional agent which is an agent of treating mood disorder. Cassano et al. does not teach or suggest the use of exo-S-mecamylamine for

treating refractory major depression. The combined references do not render obvious the claimed invention.

Accordingly, withdrawal of this rejection is respectfully requested.

CONCLUSION

A Notice of Allowance is respectfully requested. The Examiner is requested to call the undersigned at the telephone number listed below if this communication does not place the case in condition for allowance.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, the Director is hereby authorized to charge any deficiency or credit any overpayment in the fees filed, asserted to be filed or which should have been filed herewith to our Deposit Account No. 23/2825, under Docket No. Y0087.70013US01, from which the undersigned is authorized to draw.

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Respectfully submitted,

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